HYPOTHYROXINEMIA AND PHENYTOIN TOXICITY: A VICIOUS CIRCLE

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SUMMARY

Phenytoin is a widely used anticonvulsant which has a relatively narrow therapeutic range of serum concentrations, 40-80 mmol/l (10-20 mg/l). Phenytoin is known to show concentration-dependent kinetics within this therapeutic range. Because of this, small changes in dose and minor alterations in hepatic metabolism of phenytoin may cause a disproportionately large affect on serum concentrations. Hypothyroidism is associated with inhibition of hepatic oxidative metabolism of many drugs. However, there is a general consensus in the literature that serum phenytoin clearance is not influenced by thyroid functional status. This report describes a 63 year-old female who developed decreased serum free T_4 (8 pmol/l) and phenytoin toxicity. We identified three other similar case reports. We propose that the following vicious circle may be involved in this interaction: induction by phenytoin of hepatic enzymes involved in the metabolism of T_4 and T_3, decreased serum free T_4 levels causing decreased activity of hepatic NADPH cytochrome P-450 reductase, a resultant decrease in hepatic P-450 IIC9 catalyzed hydroxylation of phenytoin, increased serum phenytoin concentrations and further induction of T_4 and T_3 hepatic metabolism.

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KEY WORDS

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INTRODUCTION

Phenytoin has been widely used as an anti-epileptic medication since its introduction for treatment of grand mal seizures in 1938. Phenytoin has a relatively narrow therapeutic range of 40-80 mmol/l (10-20 mg/l) and its elimination exhibits zero-order or concentration-dependent kinetics at concentrations within this therapeutic range. This zero-order elimination is due to saturation of phenytoin hydroxylation catalyzed by hepatic cytochrome P-450 IIC9, the major route of phenytoin metabolism /1/. There are many drugs known to alter hepatic metabolism of phenytoin, resulting in increased or decreased serum phenytoin levels /2/. Because of this, introduction of new medications or dose changes of existing medications during existing phenytoin therapy requires close monitoring of serum phenytoin concentrations. Phenytoin toxicity is characterized by ataxia, nystagmus, slurred speech, decreased coordination and confusional states such as delirium and psychosis.

Hypothyroidism results in decreased metabolism of many different drugs (reviewed in /3/). Even though it is known that serum phenytoin concentrations can be greatly affected by many other drugs and that thyroid dysfunction affects hepatic oxidative metabolism of several drugs, there is a general consensus in the literature that thyroid dysfunction does not alter phenytoin disposition. This view is largely based on a published study /4/ which did not detect any alteration in phenytoin metabolism before and after treatment of nine hyperthyroid and seven hypothyroid patients.

CASE REPORT

We report a 63 year-old female who presented with phenytoin toxicity and a low serum free T_4 concentration. This patient was brought to the emergency room due to the progressive development of confusion and unsteadiness, which was particularly noticeable in the morning. This had resulted in three falls within the last three days. Physical examination revealed mild confusion, ataxia, and horizontal nystagmus. She lived in a nursing home and had a history of partial

complex seizures, approximately five per month, and a chronic psychiatric condition manifested by intermittent auditory hallucinations. Her medications were administered and documented regularly by nurses and included phenytoin (200 mg in the morning and 300 mg at bedtime), trifluoperazine (10 mg three times a day), misoprostol (200 μg three times a day), clobazam (5 mg twice daily), naproxen (250 mg three times a day), valproic acid (375 mg three times a day) and acetaminophen/codeine (325/30 mg; 1-2 tablets three times a day). There had been no changes in any of her medications for at least three months, and for the past seven months she had been receiving a regular dose of 500 mg phenytoin per day without problem. Her serum phenytoin concentrations had been stable (ranging from 54 to 60 mmol/l) for at least 5 months before her admission. One and a half months prior to admission the serum phenytoin concentration was 60 mmol/l and the serum valproic acid concentration was 189 μmol/l. Five days prior to admission, because of the onset of symptoms, her serum phenytoin concentration was measured and found to be 75 mmol/l. Because this was in the normal range, her symptoms were presumed not to be related to phenytoin. Blood analysis on admission revealed: serum phenytoin, 113 mmol/l; valproic acid, 97 μmol/l (therapeutic 350-700 μmol/l); albumin, 37 g/l (normal 35-50 g/l) and free T_4, 8 pmol/l (normal 11-22 pmol/l). Phenytoin toxicity and probable hypothyroidism were diagnosed; phenytoin was stopped for one day, the dose was decreased to 400 mg at bedtime and L-thyroxine was started at 0.1 mg p.o. daily. Her symptoms resolved rapidly.

As indicated above, at the time of admission she had low serum free T_4 levels. This patient had had a partial thyroidectomy as a child and her thyroid function, last checked 11 months earlier, was normal, TSH 1.76 mU/l (normal 0.5 to 5.0 mU/l). We believe that this patient gradually became hypothyroxinemic over the one and a half months prior to her admission and that this hypothyroxinemia resulted in the observed phenytoin toxicity.

DISCUSSION

A review of the literature revealed three other cases of phenytoin toxicity associated with hypothyroidism /5-7/. In each of these cases, as in the present report, there appeared to be no other explanation for the phenytoin toxicity other than detection of an unexpectedly low serum free T_4. In the only clinical study on this topic /4/, nine hyper-

thyroid and seven hypothyroid patients were given a single 100 mg dose of ^{14}C-labeled phenytoin before and after treatment producing a euthyroid state. Kinetics were calculated from the disappearance of radioactivity from serum. Hyper- and hypothyroidism were not associated with a change in calculated phenytoin half-life, volume of distribution or metabolic clearance. The results of this study are of questionable relevance to the clinical setting because: 1) saturation of phenytoin metabolism, common in the clinical setting, would not be present with a single 100 mg dose of phenytoin and 2) disappearance of ^{14}C-label may not be an accurate measure of phenytoin *p*-hydroxylation.

The major route of metabolism of phenytoin is *p*-hydroxylation by hepatic P-450 monooxygenase IIC9. The enzyme NADPH cytochrome P-450 reductase regenerates the active form of all P-450s by transfer of electrons from NADPH to P-450 monooxygenases. Animal studies have demonstrated that T_4 controls NADPH cytochrome P-450 reductase activity; NADPH cytochrome P-450 reductase activity is decreased in the presence of low serum T_4 and increased in the presence of high serum T_4 /8/. The observed decrease in hepatic phenytoin clearance seen in this patient could therefore be related to the low serum T_4 causing a decrease in NADPH cytochrome P-450 reductase activity and resulting in a decreased P-450 IIC9 activity.

We recognize that activity of specific cytochrome P-450s (such as cytochrome P-450 IIC9) may also be decreased by low serum free T_4, in addition to decreased activity of NADPH cytochrome P-450 reductase. However, we are unaware of evidence supporting thyroid regulation of P-450 IIC9.

Phenytoin is a known hepatic enzyme inducer. Through this mechanism phenytoin can lead to a decrease in serum concentration of other drugs, including valproic acid /2/, which probably happened in this case. This interaction would not have any impact on the interaction between phenytoin and thyroxine.

Initiation of phenytoin therapy can result in increased metabolism and decreased serum levels of thyroid hormones /9/. If the serum thyroid hormone concentration is lowered significantly, this will normally result in a compensatory increase in TSH and thyroid hormone secretion to maintain euthyroidism. In fact, most individuals taking phenytoin are euthyroid and do not show abnormally elevated serum TSH levels /10/. However, we propose that in susceptible individuals, the hypothalamic pituitary thyroid axis could be unable to compensate completely. This would allow T_4 levels to fall, causing decreased

NADPH cytochrome P-450 reductase activity, decreased phenytoin metabolism and increased phenytoin levels. As phenytoin serum levels increased, thyroid hormone metabolism would be further induced causing a vicious circle (Fig. 1).

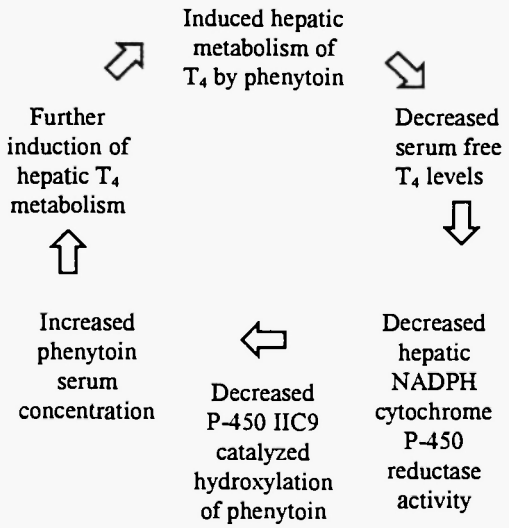

Fig. 1: Proposed "vicious circle" for hypothyroxinemia-induced phenytoin toxicity.

In addition to patients with compromised hypothalamic pituitary thyroid axis function, individuals requiring regular thyroid replacement therapy in whom phenytoin is instituted are also at risk of developing decreased serum free T_4 levels. Such patients should have thyroid function assessed six to eight weeks after starting phenytoin.

Because phenytoin elimination may follow zero-order kinetics in the therapeutic range, a minor inhibition of metabolism can result in a disproportionate increase in serum concentration of phenytoin resulting in phenytoin toxicity. Based on our hypothesis, a patient on long-term phenytoin therapy is in a state of equilibrium of phenytoin and thyroid hormone metabolism. An offset of this equilibrium by hypothyroxinemia sets in motion a vicious circle which can result in phenytoin toxicity. Treatment of this condition consists of reducing the phenytoin dose and introducing thyroxine replacement therapy, with the expectation that as normal serum thyroxine levels are achieved, the phenytoin

dose may have to be increased back to that given prior to onset of hypothyroidism.

In conclusion, the requirements for the potential vicious circle we have proposed between phenytoin and hypothyroxinemia are particularly likely to occur in elderly patients with limited thyroid reserve. It is therefore important to monitor thyroid function in patients taking phenytoin, particularly if there are suspicious symptoms or an unexplained increase in phenytoin serum levels.

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